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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,102	05/01/2001	Dennis A. Carson	220002062900	5759

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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/847,102	**Applicant(s)** CARSON ET AL.	
	Examiner MISOOK YU, Ph.D.	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 01 February 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-8,16,28 and 29*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

MISOOK YU, Ph.D.
Primary Examiner
Art Unit: 1642

Continuation of 11. does NOT place the application in condition for allowance because: For new matter rejection, Applicant argues that the support is in original claims 1 "A purified antibody for modulating a biological activity of a malignant cell that expressed a frizzled receptor, wherein said antibody binds to at least one epitope in an extracellular domain of the frizzled receptor expressed in the malignant cell" and 10, which recited the sequence identifier. Applicant also argues the specification at page 22, lines 3-6 have support for "negative effect on the malignancy" This argument has been fully considered but found unpersuasive. Although original claims 1 and 10 have support for an antibody binding to SEQ ID NO: 68, and modulates a biological activity of a malignant cell that express a frizzled 5 receptor, the specification as originally filed does not have support for the antibody inhibits growth of the malignant cell, or" antibody is effective for immunotherapy of a malignant cell that overexpresses the frizzled 5 receptor". For the specification at page 22, the specification discloses the definition "modulating a biological activity of a malignant cell" by antibody involved with Wnt/frizzled signaling pathway. However, the specification as originally filed does not say the antibody that binds to the amino terminal of SEQ ID NO: 68 inhibits growth of the malignant cell that express the frizzed 5 receptor.

As for the art rejection, Applicant argues that the invention is based on the recognition that frizzled 5 is overexpressed in some cancers, thus can be used as tumor specific antigens and the claimed antibodies are immunotherapy agents used to inhibit growth of cancer cells. This argument is not persuasive because applicant argument is not commensurate in scope of the claims. The specification at page 25 (Examples 1 and 2) discloses that frizzled 2 is overexpressed in cancer cells, while frizzled 5 is expressed both in normal and cancer cells (see Table III). In addition, Examples 3-6, at beginning page 26 of the specification discloses anti-frizzled 2 antibody inhibits growth of cancer cells. The claimed invention is drawn to antibody to frizzled 5, not frizzled 2.

Applicant argues that none of the cited references provide evidence that the frizzled 5 protein is overexpressed in malignant cells or that antibodies directed against are useful to kill cancer cells. Applicant argues the Office assumes that all wints and frizzled proteins have assigned function, and this assumption is incorrect. Applicant argues with Exhibit A (Wong et al), which shows that wnt 5a had no transforming activity. These arguments have been fully considered but found unpersuasive. As stated in the previous Office action, Tanaka et al., teach (note page 10164, right column under the heading Cloning of the Human FZ Genes, and also page 10165, left column under the heading "Identification of Human Esophageal Carcinoma-Specific Fz Gene) that the frizzled 5 receptor protein comprising instant SEQ ID NO: 68 is isolated from a human esophageal carcinoma tissue. Note the sequence alignment provided with the Office action mailed on 08/04/2003. This clearly indicates that a malignant esophageal cell express the human frizzled 5 protein. Tanaka et al., at the paragraph bridging pages 10164-5 teach that N-terminal extracellular domain of a frizzled receptor lies just before the first transmembrane helix, also teach "the ectodomain of Fz functions as natural antagonist of Fz-mediated signal transduction". Tanaka et al., at page 10164 teach Wnt binds to Frizzled family of seven-transmembrane proteins, and the seven-transmembrane proteins frizzled family proteins act as receptors for "Wnt oncoprotein" (see page 10164, left column) This suggests frizzled member proteins in tumor development and importance of extracellular domain of frizzled receptor for receptor-mediated signal for wnt-mediated oncogenic process. This disclosure is similar to the instant specification, which show a member of frizzled protein (i.e. frizzled 2) being involved in the development of cancer.

Applicant argues that Hudziak patent does not suggest that any protein with an extraceullar ligand binding domain is suitable candidate to raise antibodies, and provide no motivation or expectation of success that antibodies against fzdt would inhibit growth of malignant cells. This argument has been fully considered but found unpersuasive. Hudziak patent teaches at column 5, lines 16 and 17, "antibodies to inhibit the growth of tumor cells"; at column 6 lines 5-13 "Advantageously antibodies are selected which greatly inhibit the receptor function by binding the steric vicinity of the ligand binding site of the receptor (blocking the receptor), and/or which bind the growth factor in such a way as to prevent (block) the ligand from binding to the receptor. These antibodies are selected using conventional in vitro assays for selecting antibodies which neutralize receptor function." This suggests that an antibody binding to extracellular domain, where the natural ligand binds to, would inhibit the function of the receptor. Hudziak patent also teaches assays to screen an antibody that inhibits growth of the malignant cell. Hudziak patent teaches a cytotoxic response and label at claims 1-39.

Therefore one of ordinary skill would have been motivated to screen an antibody binding to the extracellular domain (i.e. the natural ligand binding site) of frizzled 5 protein, which is expressed on a malignant cell as taught by Tanaka et al., wherein the antibody inhibits the growth of the malignant cells since the screening assay is taught by Hudziak patent. It would have been obvious to one of ordinary skill in the art to make and use an antibody directed the extracellular domain of a receptor because of the advantage as taught by the Hudziak patent. Further, one of ordinary skill would be motivated to screen an antibody inhibiting cancer cells because this kind of antibody could be used in cancer treatment as taught by Hudziak patent, and cancer treating antibody would make money.

In addition, based on Noelle v. Lederman, 69 USPQZd 1508, 1514 (Fed. Cir. 2004), an antibody to known antigenic sequence is obvious, and one of skill would have been arrived at the claimed invention with a reasonable expectation of success, given the amino acid sequence has been known, the extracellular domain of a frizzled 5 is where the natural ligand binds to, had been well known in the art before the effective filing date of the instant application as taught by Tanaka et al., and also given that advantage of the antibody to extracellular domain and an assay to isolated an antibody inhibiting the growth of a malignant cell had been known in the art as taught by Hudziak patent well before the effective filing date of the instant application.

MISOOK YU
PRIMARY EXAMINER